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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/692,623	10/20/2000	Stephen M. Boyle	031786-046	2200

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EXAMINER	
GRASER, JENNIFER E	

ART UNIT	PAPER NUMBER
1645	12

DATE MAILED: 02/25/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Advisory Action

Application No.	Applicant(s)
09/692,623	Boyle
Examiner	**Art Unit**
Jennifer Graser	1645

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

THE REPLY FILED *Feb 6, 2003* FAILS TO PLACE THIS APPLICATION IN CONDITION FOR ALLOWANCE. Therefore, further action by the applicant is required to avoid the abandonment of this application. A proper reply to a final rejection under 37 CFR 1.113 may only be either: (1) a timely filed amendment which places the application in condition for allowance; (2) a timely filed Notice of Appeal (with appeal fee); or (3) a timely filed Request for Continued Examination (RCE) in compliance with 37 CFR 1.114.

THE PERIOD FOR REPLY [check only a) or b)]

a) ☒ The period for reply expires *3* months from the mailing date of the final rejection.

b) ☐ In view of the early submission of the proposed reply (within two months as set forth in MPEP § 706.07 (f)), the period for reply expires on the mailing date of this Advisory Action, OR continues to run from the mailing date of the final rejection, whichever is later. In no event, however, will the statutory period for the reply expire later than SIX MONTHS from the mailing date of the final rejection.

Extensions of time may be obtained under 37 CFR 1.136(a). The date on which the petition under 37 CFR 1.136(a) and the appropriate extension fee have been filed is the date for purposes of determining the period of extension and the corresponding amount of the fee. The appropriate extension fee under 37 CFR 1.17(a) is calculated from: (1) the expiration date of the shortened statutory period for reply originally set in the final Office action; or (2) as set forth in (b) above, if checked. Any reply received by the Office later than three months after the mailing date of the final rejection, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

1. ☐ A Notice of Appeal was filed on _____. Appellant's Brief must be filed within the period set forth in 37 CFR 1.192(a), or any extension thereof (37 CFR 1.191(d)), to avoid dismissal of the appeal.

2. ☒ The proposed amendment(s) will be entered upon the timely submission of a Notice of Appeal and Appeal Brief with requisite fees.

3. ☐ The proposed amendment(s) will not be entered because:

(a) ☐ they raise new issues that would require further consideration and/or search. (See NOTE below);

(b) ☐ they raise the issue of new matter. (See NOTE below);

(c) ☐ they are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal; and/or

(d) ☐ they present additional claims without cancelling a corresponding number of finally rejected claims.

NOTE: _____

4. ☐ Applicant's reply has overcome the following rejection(s):

5. ☐ Newly proposed or amended claim(s) _____ would be allowable if submitted in a separate, timely filed amendment cancelling the non-allowable claim(s).

6. ☒ The a) ☐ affidavit, b) ☐ exhibit, or c) ☒ request for reconsideration has been considered but does NOT place the application in condition for allowance because:
See attached.

7. ☐ The affidavit or exhibit will NOT be considered because it is not directed SOLELY to issues which were newly raised by the Examiner in the final rejection.

8. ☒ For purposes of Appeal, the status of the claim(s) is as follows (see attached written explanation, if any):

Claim(s) allowed: *none*

Claim(s) objected to: *28-30 (depend from rejected claims)*

Claim(s) rejected: *24-27*

9. ☐ The proposed drawing correction filed on _____ a) ☐ has b) ☐ has not been approved by the Examiner.

10. ☐ Note the attached Information Disclosure Statement(s) (PTO-1449) Paper No(s). _____

11. ☐ Other:

J. Graser 2/21/03

JENNIFER GRASER
PRIMARY EXAMINER
ART UNIT 1645

ADVISORY ACTION

Acknowledgment and entry of the Amendment submitted 2/6/03, Paper No. 11 is made. Claims 24-30 are currently pending and under examination.

1. The references listed on the PTO-1449 previously submitted on 7/31/02 have been placed in the file. However, a PTO-1449 form did not accompany these references. It is the PTO's policy to line through in ink all references not considered when an IDS does not conform to the requirements. The copy of the previously submitted PTO-1449 form, submitted on 7/31/02, was lined through and indicated as not considered. As stated in the Final rejection, the date of any re-submission of any item of information contained in this information disclosure statement or the submission of any missing element(s) will be the date of submission for purposes of determining compliance with the requirements based on the time of filing the statement, including all certification requirements for statements under 37 CFR 1.97(e). See MPEP § 609 ¶ C(1). Accordingly, the information disclosure statement filed 2/6/03 fails to comply with 37 CFR 1.98(a)(1), which requires a list of all patents, publications, or other information submitted for consideration by the Office. It has been placed in the application file, but the information referred to therein has not been considered.

Claim Rejections - 35 USC § 103

2. Claims 24-27 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Kontinen et al (WO 94/19471) and Highlander et al. (US 6,180,112) for the reasons set forth in the prior Office Action, mailed 11/19/02.

Response to Applicants' Arguments:

In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). Although Kontinen et al does suggest the use of vaccines and pharmaceuticals, it does not particularly exemplify the use of the recombinant bacterium as the vaccine, but instead suggests the use of its over-expressed products. Kontinen teaches a method and expression system for enhancing secretion of hyperproduced homologous and heterologous exoproteins in bacteria. It is specifically taught that methods for overexpressing secreted proteins were readily available in the prior art, such as increasing gene expression by using multicopy plasmids to overexpress a desired antigen or enhancing the activity of the gene by modifying its regulatory elements, e.g., by using strong promoters or multiple promoters (as in Highlander et al), resulting in dramatic increases in the synthesis of exoproteins. See page 4, lines 15-20. It is taught that these products may be used as vaccines which by definition would confer protective immunity to a host.

They further argue that the secondary reference, Highlander et al, teaches over-expression of an activator of the leukotoxin polypeptide not the leukotoxin polypeptide itself. This is true. Highlander et al was cited to demonstrate that over-expressing strains of bacterium could be used as whole cell vaccines. The primary reference teaches that these over-expressing strains could be made in different ways which would achieve the same end result, i.e., homologous over-

expression of a desired antigen. Highlander et al. discloses whole cell vaccine compositions comprising a recombinant, avirulent *Pasteurella haemolytica* organism which comprises a strong leukotoxin promoter which allows for homologous overexpression of said leukotoxin antigen. The *P.haemolytica* transcriptional activator is introduced on a multicopy plasmid (see bottom of column 42 and claim 8). It is specifically taught that since *P.haemolytica* leukotoxin genes are poorly expressed in *E.coli*, Pasteurella-specific transcriptional factors were used for this homologous, overexpression. Both methods and vaccine for the immunization, prophylaxis or treatment of vertebrates suffering from disease caused by *P.haemolytica* are specifically taught. The prior art teaches that the use of multicopy plasmids and/or using strong promoters or multiple promoters was well known in the bacterial art for increasing the production of a desirable protein product. The prior art also teaches that recombinant whole cell vaccines were well known.

The two references taken together provide motivation for using a whole cell vaccine with homologous over-expression. Kontinen teaches a method and expression system for enhancing secretion of hyperproduced homologous and heterologous exoproteins in bacteria. It is specifically taught that methods for overexpressing secreted proteins were readily available in the prior art, such as increasing gene expression by using multicopy plasmids to overexpress a desired antigen or enhancing the activity of the gene by modifying its regulatory elements, e.g., by using strong promoters or multiple promoters (as done in Highlander et al.), resulting in

dramatic increases in the synthesis of exoproteins. Highlander et al teach homologous over-expression of a desired antigen in an attenuated strain of Gram-negative bacteria and the use of this strain as a vaccine. Taken with Kontinen, it would have been obvious to one of ordinary skill in the art that the over-expression of leukotoxin taught by Highlander et al. could have also been achieved by the using multicopy plasmids to overexpress the desired protein instead of just using a multicopy plasmid comprising many copies of its activator. Kontinen teaches that both methods provide the same result, overexpression of a desired protein. It would have been obvious to one of ordinary skill in the art at the time the invention was made that not only Gram-positive bacterium, but also attenuated or avirulent Gram-negative bacterium, as evidenced by Highlander et al., could be used to produce an homologous and/or homologous-heterologous expression system for the purpose of producing a vaccine. Highlander et al teaches that the expression system, itself, and not just the isolated expression products make effective vaccines.

Allowable Subject Matter

3. Claims 28-30 are free of the prior art. However, they are dependent from a rejected claim and must be rewritten to include all of the limitations of the base claim and any intervening claims.

4. Correspondence regarding this application should be directed to Group Art Unit 1645. Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15,1989). The Group 1645 Fax number is (703) 308-4242 which is able to receive transmissions 24 hours/day, 7 days/week.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jennifer E. Graser whose telephone number is (703) 308-1742. The examiner can normally be reached on Monday-Friday from 7:00 AM-4:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Lynette Smith, can be reached on (703) 308-3909.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.